Thyroid (dys)function in critically ill patients

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Abstract

Patients at the Intensive Care Unit (ICU) typically present with decreased plasma triiodothyronine (T3), low thyroxine (T4), and normal range or slightly decreased thyroid stimulating hormone (TSH) . This ensemble of changes is collectively known as the non-thyroidal illness syndrome (NTIS). The extent of the NTIS correlates with prognosis, but there is no proof for causality of this association. Initially, NTIS reflects the acute phase response to systemic illness as well as macronutrient restriction, and may be beneficial. The pathogenesis of NTIS in prolonged critical illness is more complex and includes suppressed hypothalamic thyrotropin releasing hormone (TRH) production, explaining persistently reduced TSH secretion in spite of low plasma TH. In some cases it is difficult to distinguish between NTIS and severe hypothyroidism which is a rare primary cause for ICU admission. Infusing hypothalamic releasing factors can reactivate the thyroid axis in patients with NTIS, inducing an anabolic response. If this approach carries clinical benefit in terms of outcome is currently unknown. In this review, we will discuss diagnostic aspects, pathogenesis and implications of NTIS as well as its distinction from severe primary thyroid disorders in ICU patients.

Introduction

The hypothalamus–pituitary–thyroid (HPT) axis is controlled by a classical endocrine feedback loop. Thyrotropin-releasing hormone (TRH) is released at the level of the hypothalamus which stimulates the anterior pituitary to secrete thyroid stimulating hormone (TSH). In turn, TSH drives the thyroid gland to release thyroid hormones (TH). The prohormone thyroxine (T4) is converted in peripheral tissues to the active hormone triiodothyronine (T3). Hypothalamic TRH neurons were identified as determinants of TH setpoint regulation over three decades ago, and this was followed by the demonstration of a key role played by thyroid hormone receptor (TR) β in TH negative feedback both at the level of the hypothalamus and anterior pituitary. Thus, the HPT axis was assumed to have a fixed setpoint, aiming at individually determined TH serum concentrations. [1] However, more recent studies showed that TH serum concentrations can be variable and adaptive in response to environmental factors, including the nutrient availability and inflammatory stimuli [2].
Marked changes in TH plasma concentrations have been observed in a variety of diseases, characterized by clearly decreased plasma T3, low plasma T4, and increased plasma reverse T3 (rT3) concentrations. In spite of the low T3 and T4, TSH is typically within the normal range or slightly decreased. This ensemble of changes in thyroid function tests is collectively known as the "non-thyroidal illness syndrome" (NTIS). [3] The presentation, pathogenesis, metabolic consequences, and clinical management of thyroid dysfunction in critically ill patients will be the focus of the current review. The distinction between NTIS in ICU patients and primary thyroid disorders in ICU patients can sometimes be difficult, and will be briefly touched upon as well.

Description of Nonthyroidal illness

Both in humans and rodents, illness decreases TH serum concentrations without a concomitant rise in serum TSH. This reflects a deviation from "normal" negative feedback regulation in the HPT axis. Should a similar drop in serum T3 and T4 occur in the context of primary hypothyroidism, serum TSH would be markedly elevated and the patient would be in need of treatment with TH replacement therapy. The combination of low serum T3 and serum TSH within the reference range in the context of illness is called NTIS.[3 4] Several alternative names have been used to refer to NTIS, including the "sick euthyroid syndrome" and the "low T3 syndrome" [5], the latter term pointing to low plasma T3 as the most consistent and striking alteration; in this review we will use the term NTIS.
Very rapidly after the onset of acute stress, such as myocardial infarction or surgery, serum T3 decreases. In patients undergoing abdominal surgery, a fall in serum T3 was observed already after 2

hours. [6] NTIS has been reported in patients with acute and chronic illnesses, including infectious diseases, cardiovascular and gastrointestinal diseases, cancer, burns and trauma. [4] Serum T3 decreases further as the severity of the disease progresses. This is reflected in the reported correlations between the size of a myocardial infarction, the increase in serum creatinine in renal insufficiency and burn severity on the one hand, and the fall in serum T3 on the other hand. [4] Therefore, the magnitude of the drop in plasma TH levels generally reflect the severity of the condition and as a consequence, could have prognostic significance. In one study performed in ICU patients, the sensitivity and specificity in predicting mortality were 75% and 80%, respectively, for serum T4 <40 nmol/L .[7] For combined low serum T4 and high serum cortisol these number were even higher, i.e., 100% and 81%. Likewise, low T3 was shown to be a strong predictor of mortality in patients with heart disease. [8]

NTIS is present in most, if not all, in critically ill patients, which can be defined as any life-threatening condition that requires support of vital organ function without which death would be imminent. [9] Thus, critically ill patients that require prolonged treatment in the intensive care unit (ICU) typically exhibit decreased plasma T3 and T4 concentrations. An absent TSH response in this context points to profoundly altered HPT axis feedback regulation. [10] Although the normal TSH level in the presence of the low plasma T3 concentrations has been interpreted as indicating a “euthyroid” status, this assumption has not been substantiated by experimental data. The typical changes in plasma TH parameters that can be easily assessed in the clinical setting are the result of alterations in the central regulation of the thyroid axis, including decreased TSH pulsatility. [10] Moreover, several alterations occur in the peripheral components of the thyroid axis that vary according to the tissue as well as the severity of illness. [11] The peripheral changes include, but are not limited to, altered concentrations of the TH binding proteins and TH transporters, changes in the expression and activity of the TH deiodinases and alterations in TH receptor expression. [3] Changes in thyroid parameters that are similar, but not identical to those observed during NTIS, occur in response to fasting in healthy subjects [12]. The NTIS in response to fasting in healthy subjects is regarded adaptive and beneficial by reducing energy expenditure to limit catabolism via decreased TH action.

At present it is unknown if the NTIS occurring in response to critical illnesses should be seen as an adaptive mechanism, such as in starvation, or rather as a maladaptive mechanism. On one hand, it seems logical to assume that a reduction in serum T3 would decrease TH action in important T3 target organs such as liver and muscle, thereby affecting metabolism which might be beneficial in critically ill patients. On the other hand, one might argue that patients with prolonged critical illness show clear symptoms and signs that resemble those observed in hypothyroidism, including impaired consciousness and myocardial function, hypothermia, neuropathy and muscle weakness, as well as atrophy of the skin and hair loss, which together might impede recovery. [13,14] Although the

hypothesis that NTIS in ICU patients could be maladaptive has been discussed extensively [9] surprisingly few clinical studies (in part RCTs) aimed at modulating NTIS in order to improve clinical outcome have been published. When considering clinical intervention studies, irrespective of their design, the risk-benefit ratio may seem favorable with a majority showing benefit and only a minority showing harm, but this ratio cannot really be assessed when considering only RCTs with clinically relevant outcome measures such as mortality or morbidity (see Table 1).

Pathogenesis of NTIS

A) Altered HPT axis feedback regulation and local TH metabolism

Severe illness induces profound alterations in thyroid hormone economy resulting in a down-regulation of the HPT axis both at the hypothalamic and pituitary level in association with a decrease in circulating TH concentrations. [3] This observation points to marked alterations in negative feedback regulation in the HPT axis during NTIS. [2] The central down regulation of the HPT-axis during NTIS in humans was confirmed by the observation in autopsy samples of decreased TRH gene expression in the hypothalamic paraventricular nucleus (PVN) of patients with NTIS. The observed TRH mRNA expression in the PVN showed a positive correlation with pre-mortem plasma TSH and T3. [15] In addition, simultaneous changes in liver thyroid hormone metabolism contribute to the characteristic changes in plasma thyroid hormones levels: low plasma T3 and high plasma rT3, normal or low-normal plasma TSH, and -during severe illness- low plasma T4. [3]

Although the mechanisms involved in these seemingly paradoxical HPT axis changes are only incompletely understood, animal studies using a variety of NTIS models have elucidated some aspects of the pathogenesis of NTIS. NTIS induces specific alterations in enzymes involved in TH metabolism (deiodinases type 1, 2 and 3 or D1, D2 and D3), TH transporters and TH receptors (TRα and TRβ). [3] For example, the induction of acute inflammation in rodents by a single peripheral injection of bacterial endotoxin or lipopolysaccharide (LPS) stimulates D2 mRNA expression in tanycytes lining the third ventricle in the hypothalamus. [16,17] Conceivable, this D2 upregulation is followed by an increased local production of T3, which subsequently lowers TRH mRNA expression in the PVN as observed in humans (see figure 1). [15,18,19] Although an increase in D2 activity has not been proven yet, experiments in an *in vitro* co-culture system confirmed that glial D2 modulates T3 concentrations and gene expression in neighboring neurons. [20] Thus, inflammation inhibits hypophysiotropic TRH neurons probably via increased D2 activity thereby explaining the hypothalamic down regulation of the HPT axis during NTIS.

In the periphery, the liver is one of the key TH metabolising organs. It expresses the TH transporters monocarboxylate transporter 8 (MCT8) and monocarboxylate transporter 10 (MCT10), both D1 and D3 (although D3 is expressed at very low levels in a healthy liver) and the TRβ1 as well as TRα1 [a more detailed overview of cellular thyroid hormone metabolism is given in figure 2]. Although liver D1 contributes only for approximately 20% of the circulating T3 in humans, [21] its involvement in the pathogenesis of the NTIS has been extensively studied. [22] Human studies showed reduced liver D1 mRNA expression and enzyme activity during illness, suggesting a role for liver D1 in the pathogenesis of illness induced changes in plasma T3 and rT3. [22]

Critical illnesses that include a significant hypoxia/ischemia component exhibit a significant increase in TH catabolism via induction of D3. This has been shown originally in post-mortem tissues of ICU patients [23] and later in a series of animal models including myocardial [24] and brain infarction. [20] Thus, it is likely that induction of D3 during NTIS in tissues that normally express no, or only very little D3 contributes significantly to the abnormalities in thyroid economy observed during ischemic injury. [25]

B) NTIS is part of the acute phase response

Several clinical studies performed more than 20 years ago showed a clear relationship between the changes in thyroid hormone metabolism and the activation of a variety of pro-inflammatory cytokines. [26,27] Cytokines are important mediators of the acute phase response affecting fever, leucocytosis, the release of stress hormones and the production of acute phase proteins. Cytokines are also able to affect the expression of many proteins involved in thyroid hormone metabolism and are causally involved in the pathogenesis of NTIS. [28] LPS stimulation of a variety of cells results in a strong inflammatory response characterized by the production of a variety of cytokines including Tumor Necrosis Factor α (TNFα), Interleukin-1 (IL-1), and Interleukin-6 (IL-6). For the induction of cytokines the activation of inflammatory signaling pathways is mandatory, including nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) and activator protein (AP)-1. [29] It was recently shown that activation of NFκB plays an important role in the upregulation of D2 in hypothalamic tanycytes during inflammation. [30, 31] D1 is also sensitive to cytokines; D1 expression in a liver cell line decreases upon IL-1β stimulation and this response can be abolished by simultaneous inhibition of NFκB and AP-1.[32] Summarized, cytokines, activated as a result of the inflammatory response, are causally involved in the pathogenesis of NTIS, making NTIS part of the acute phase response.

C) Differential effects of illness on thyroid hormone action in metabolic organs

Energy homeostasis changes dramatically during illness, since activating the immune system involves energy expenditure at the same time when food intake is decreased. Although the common view is that NTIS results in overall down-regulation of metabolism in the organism in order to save energy, recent work has shown great variability between various key metabolic organs and tissues in the expression of genes encoding proteins involved in thyroid hormone (TH). [3] Interestingly, these tissues included cells that until recently were not known to be TH responsive such as granulocytes, [33] macrophages [34] and lung epithelial cells (see figure 4). [35]

Thyroid hormones are important for skeletal muscle function as a variety of genes expressed in muscle are regulated by T3. TH signalling was shown to be altered in skeletal muscle tissue during illness depending on the type (acute inflammation or bacterial sepsis) and stage (acute or prolonged) of illness. [36-38] It is unknown at this stage whether the differential alterations in muscle thyroid hormone metabolism during illness are clinically relevant, although muscle dysfunction has been associated with changes in muscle thyroid hormone metabolism during prolonged critical illness. [39-42]

Recently it has become clear that TH target cells/organs respond to inflammation by increasing D2 or D3 expression, thereby affecting cellular function. For example, stimulation of macrophages with bacterial endotoxin increases D2 expression, which was shown to be essential for cytokine production and phagocytosis. [34] Moreover, granulocytes show marked D3 expression when infiltrating an infected organ. [43] A functional role for this phenomenon was suggested by the observation that the lack of D3 in mice severely impairs the bacterial clearance capacity of the host. [44] The induction of D3 in activated granulocytes not only inactivates thyroid hormone but also yields substantial amounts of iodide which may be used by the cell for bactericidal and tissue-toxic systems. [45] Summarized, the presence of D3 in activated granulocytes suggests a novel (and protective) role for the deiodinating enzymes in the defense against acute bacterial infection.

D) The role of nutrition (see figure 3)

Critical illness is associated with loss of appetite and poor oral and enteral nutritional intake. [46] As fasting in healthy subjects induces a similar NTIS response as observed in critically ill patients, [12] decreased caloric intake during illness might contribute to the development of NTIS in a major way. The mechanism by which fasting induces a decrease in serum TH is multifactorial and includes a decrease in serum leptin, and downregulation of hypothalamic hypophysiotropic TRH neurons contributing to persistently low serum TSH. [47] At the organ level, there is decreased activity of the deiodinase type-1 (D1), the enzyme driving the conversion of T4 into the biologically active T3 and clearing the biologically inactive reverse T3 (rT3). Increased activity of type-3 deiodinase (D3), the T3

inactivating enzyme, has also been reported. [48] Three clinical studies comparing patients under different nutritional strategies indeed indicated that decreased caloric intake during critical illness is associated with a more pronounced NTIS. [49-51]

Recently, the large randomized controlled EPaNIC trial compared two nutritional regimens in 4640 adult ICU patients at risk of malnutrition: the "early parenteral nutrition (PN) group" received parenteral nutrition within 48h of ICU admission to supplement insufficient enteral nutrition, whereas the "late PN group" did not start with parenteral nutrition to supplement enteral nutrition before day 8. [52] This study demonstrated that tolerating a nutritional deficit during the first week of critical illness as compared to the early administration of supplemental parenteral nutrition, resulted in fewer complications and accelerated recovery. [52] Tolerating a fasting response thus appears to be beneficial for the patient. Of interest, a subanalysis of the EPaNIC trial (n=280) demonstrated that late feeding reduced complications and accelerated recovery of patients with NTIS, but aggravated the changes in circulating levels of plasma TSH, total T4, T3, and the T3 to rT3 ratio. The opposite was observed with early feeding. [53]

Thus, the peripheral metabolism of T3 is affected by decreased nutritional intake during acute critical illness. A subanalysis of the EPaNIC trial indicated that the inactivation of T3 to rT3, as part of the fasting response, might be a beneficial adaptation during acute illness. [53] Targeting fasting blood glucose levels with intensive insulin therapy in children with critical illness to 2.8–4.4 mmol/L in infants and 3.9–5.6 mmol/L in children, thereby mimicking a fasting response, resulted in improved outcome [54] while aggravating the peripheral NTIS at the same time. Multivariate Cox proportional hazard analysis indicated that the further reduction of T3/rT3 explained part of the therapy benefit on mortality. [55]

Together, these findings suggest that thyroid economy is affected by decreased nutritional intake during acute critical illness, and the inactivation of T4 to rT3 and T3 to T2, as part of the fasting response, might be a beneficial adaptation during acute illness. [53] In particular, the acute peripheral inactivation of TH by inner ring deiodination during critical illness is likely a beneficial adaptation. Indeed, the reduced amount of circulating active T3 could be interpreted as an attempt of the body to decrease the metabolic rate and reduce expenditure of scarce energy, to prevent protein breakdown and, thereby, to promote survival. In contrast, the central lowering of T4 could be deleterious. Consistent with this interpretation is the observation that especially the more severely ill patients display a decline in circulating T4 levels, whereas virtually all ill patients display low T3 and high rT3 levels already from admission to the ICU. [36]

Diagnosis and management of severe primary thyroid disorders in ICU patients

The high prevalence of NTIS in ICU patients and the magnitude of HPT axis changes in these patients can make it difficult to distinguish NTIS from untreated primary hypothyroidism**.** Levothyroxine treatment should be continued during the ICU stay in patients previously known to have hypothyroidism. Although this practice seems trivial, prescription and continuation of chronic therapy is not always a primary focus of care in the ICU setting. A retrospective chart review study in a tertiary referral ICU showed that thyroid replacement therapy was not prescribed for more than 7 days in 17.3% of patients and omitted entirely in 3/133 patients. [56] The diagnosis of primary hypothyroidism in severely ill patients who were unknown to have hypothyroidism before admission can be difficult as serum TH, especially T3, is decreased in most ICU patients due to NTIS. In patients clinically suspected to have severe hypothyroidism, the most useful test is plasma TSH, as a normal plasma TSH virtually excludes primary hypothyroidism. In patients with a combination of primary hypothyroidism and NTIS, serum TSH is still high and responsive to levothyroxine treatment. However, it should be kept in mind that, in hypothyroid patients, the high serum TSH concentration may decrease during the acute phase of illness especially if dopamine or high doses of glucocorticoids were given. Thus, high serum TSH in combination with low serum T4 is indicative of hypothyroidism, although this combination can also be found in patients recovering from NTIS. A high serum T3/T4 ratio and a low serum rT3 favor the presence of hypothyroidism, as the ratios are opposite in NTIS, but the diagnostic accuracy of these measurements is limited. [4] Especially in patients with long-standing and untreated hypothyroidism, cold exposure, infection and vascular accidents may trigger the development of myxedema coma. This is a life-threatening condition with a high mortality of ~50%. [57] Key clinical features are hypothermia and altered consciousness, and laboratory findings include elevated TSH with low or undetectable T4 and T3. Of note, the presence of NTIS may reduce the degree of TSH elevation. Active management is important and depends on the recognition of the clinical features. The treatment of myxedema coma aims at TH replacement, treatment of the underlying condition and supportive care. In addition, stress dose glucocorticoids should be given (e.g., 100 mg hydrocortisone every 8h) as concomitant autoimmune primary adrenal insufficiency may be present, especially in patients with hypoglycemia. [58]

A low serum TSH may point to thyrotoxicosis, especially if serum FT4 is high as well. The degree of TSH suppression correlates with the likelihood of thyrotoxicosis. The combination of suppressed TSH, high FT4 and normal T3 may point to the combination of thyrotoxicosis and NTIS, and has been referred to as T4-thyrotoxicosis. [4] Needless to say, physical examination (goiter, proptosis) and the presence of thyroid antibodies (anti TPO, TBII) may give further information regarding the probability of thyrotoxicosis. In the ICU setting some patients may present with decompensated thyrotoxicosis, or thyroid storm, which is a life-threatening condition. Importantly, TH levels do not distinguish

patients with thyroid storm from those with severe thyrotoxicosis as thyroid storm is a clinical diagnosis. The classical findings include fever, (supraventricular) tachycardia, gastrointestinal symptoms, and altered mental state including confusion, delirium or even coma. [57] Precipitating factors include surgery, parturition, and infection. Therapy of thyroid storm generally requires ICU monitoring and aims at restoring thyroid gland function while diminishing TH effects on peripheral tissues using, a combination of beta-blockers, thyrostatics, i.v. glucocorticoids and eventually high-dose of iodide compounds. [59] In a recent retrospective cohort study in acutely hospitalized thyrotoxic patients, the presence of CNS dysfunction was the only significantly different clinical feature between patients with thyroid storm and patients with compensated thyrotoxicosis. Thus, thyrotoxic patients with possible thyroid storm and altered mentation should be treated aggressively with supportive measures and antithyroid drugs. [60]

Treatment/management of NTIS

The question whether interventions aimed at normalizing thyroid hormone levels in prolonged critically ill patients are beneficial has not been satisfactorily answered to date. Clinical studies reporting interventions in NTIS patients are listed in Table 1. There are only few, rather small RTCs assessing the effects of treatment with thyroid hormone in patients with NTIS. These trials report results obtained in a large variety of patient groups, e.g. patients with acute renal failure, [61] burn injury, [62] cardiac surgery, [63 - 66] and ICU patients with low T4 levels. [67] Furthermore, the age of the study population in these studies varies considerably, ranging from premature newborns to children and adults. Disease severity is another variable, ranging from critical illness at the medical ICU to heart surgery in relatively healthy subjects. Surprisingly little consistency is present in the choice of the active study drug, as both T3 (orally as well as iv) and levothyroxine (LT4) have been used. In the context of studies with T4 or T3, it should be kept in mind that normalizing TH levels in serum does not necessarily result in normal tissue concentrations of TH. This was clear from one study in patients with critical illness who received thyroid hormone treatment. [22] In these patients, the increase in liver T3 concentrations after thyroid hormone treatment was disproportionally high compared to the increase in serum and muscle T3 concentrations. In addition to treatment with TH, the effect of selenium (Se) on NTIS per se and on clinical outcome parameters has been studied. [68, 69] Recently, the effect of N-acetyl-cysteine (NAC), an antioxidant that restores intracellular glutathione (a co-factor required for D1 catalytic activity), on NTIS was studied in a small RCT. NAC administration appeared to prevent the derangement in thyroid hormone concentrations commonly occurring in the acute

phase of acute myocardial infarction, indicating that oxidative stress is involved in the pathogenesis of NTIS in acute MI. [70]

An unresolved and somewhat controversial issue is the question if there is a place for thyroid hormone treatment in patients with heart failure. Although the failing heart shows molecular changes partly overlapping with the hypothyroid heart, this does not necessarily imply that treatment of patients with heart failure and low serum T3 in the setting of NTIS is favorable. [8] The therapeutic use of TH in patients with heart failure has not been adequately studied, although some encouraging trials have been reported. One small RCT in patients with dilated cardiomyopathy showed beneficial effects of medium-term (3 months) levothyroxine treatment on cardiac performance, [71] while another RCT showed that the thyroid hormone analog 3,5 diiodothyropropionic acid (DITPA) improved some hemodynamic parameters albeit without evidence for symptomatic benefit in heart failure. [72]

Finally, hypothalamic neuropeptides including (combinations of) Growth Hormone Releasing Hormone (GHRH), Growth Hormone Releasing Peptide (GHRP)-2, Gonadotropin Releasing Hormone (GnRH) and TRH have been used in prolonged critically ill patients in an attempt to stimulate the anterior pituitary gland, thereby restoring endocrine function in terms of plasma concentrations and hormone pulsatility. [10,73-76] Overall, the RCTs in critical illness using T3 and/or T4 have been largely negative in terms of clinical benefit. An overview of studies including their clinical endpoints is presented in Table 1. It should be noted, however, that hypothalamic neuropeptides, notably TRH in combination with GHRP-2 iv, can restore circulating thyroid hormone concentrations as well as TSH pulsatility to a remarkable extent. In addition, this strategy improved overall metabolism, including bone markers and anabolic parameters. The interpretation of these findings as reflecting insufficient hypothalamic drive of pituitary TSH release in protracted critical illness was supported by a study in deceased patients with NTIS who appeared to have decreased hypothalamic TRH mRNA expression in the PVN, in correlation with decreased pre-mortem plasma TSH and T3 concentrations. [15] However, the studies performed with hypothalamic neuropeptides comprised only small patient numbers while at present it is unclear if treatment with those neuropeptides offers clinical benefit in terms of morbidity and mortality. In sum, no definitive conclusion about the efficacy of thyroid hormone treatment in ICU patients with NTIS can be drawn at this stage. [8]

It should be noted that aside from possible benefit, there may even be possible harm. In particular, the study by Acker *et al* in patients with acute renal failure raised some concern because of a tendency towards increased mortality after treatment with levothyroxine (see Table 1) without any beneficial effect on outcome, e.g. in terms of dialysis need. [61] However, the observed mortality in the

control group in this study was less than expected, which does not necessarily justify the interpretation that the intervention was harmful. It is evident that none of the reported studies were adequately powered to detect clinically meaningful differences. Finally, the majority of these trials used rather high doses of either T4 or T3, probably inducing further suppression of pituitary TSH release and altered tissue deiodinase activities. The use of neuropeptides, including TRH, to stimulate the HPT axis in a more physiological way, may be promising in this respect. Large RCTs in well-defined patient groups will be required to investigate possible positive effects of this approach in terms of outcome. High priority should be given to RCTs comparing the effect of the hypothalamic neuropeptides including TRH with placebo, as this approach has already been shown to partially normalize serum TH parameters while at the same time improving metabolic markers. [10] However, these effects have been shown only in small studies that were not powered to study clinically relevant outcome measures such as mortality or morbidity. Another interesting possibility will be to investigate treatment with recombinant human (rh)TSH, as this is –similar to THR- a physiological stimulus for TH release from the thyroid. A pilot study presented at the 2013 Annual Meeting of the European Thyroid Association showed that daily low dose (30 μg) TSH treatment in patients with central hypothyroidism was sufficient to cause increases of plasma TSH levels to the normal range. The treatment also improved quality of life and sleep behaviour (abstract P153, Dixit et al Eur Thyroid J 2013: 2(suppl 1)). It will be of interest to investigate if this approach can be used in ICU patients with NTIS to normalize TSH and TH, and -if so - to improve clinical outcome. Again, this should be done in adequately powered, randomized and placebo-controlled studies.

Conclusion

In the classic view, NTIS is a syndrome occurring during a variety of illnesses marked by decreased plasma TH concentrations with unclear consequences. Recent studies have shown that the alterations in thyroid economy during NTIS reflects profound and complex changes at the level of the HPT axis, in terms of setpoint regulation, and at the organ level in terms of local TH metabolism (figure 5). Whether the observed changes in critically ill patients are beneficial or deleterious in terms of outcome probably depends on disease stage and severity, the need of prolonged vital support, and environmental factors including parenteral nutrition. At present, there is no evidence-based consensus or guideline advocating thyroid hormone treatment of NTIS in the critically ill patients. Adequately powered RCTs should be performed to define whether active management of NTIS, e.g. using hypothalamic neuropeptides including TRH, may yield clinical benefit in terms of outcome.

Method

We searched MEDLINE (via Ovid, 1946 to March 2014), Embase (via Ovid, 1947 to March 2014) and the Cochrane Central Register of Controlled Trials (The Cochrane Library, 6 March 2014). The search strategy consisted of subject headings and free-text words related to the concepts "critically ill patients" or "intensive care" or "sepsis" in combination with "thyroid dysfunction" or "euthyroid sick syndrome" or "thyroid hormones". The search strategy was limited to English language publications. No publication date restrictions were applied. References that were used were selected based on title.

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Table 1: A selected overview of clinical studies reporting interventions in NTIS patients (A: children, B: adults). Y: yes and N: no, when Y is indicated in the column "beneficial/positive" the effect of treatment (defined by the authors) is positive. When Y is indicated in the column "harmful", harmful effects (defined by the authors) have been reported. GA, gestation; iv, intravenous; CNS, central nervous system; GH, growth hormone; PRL, prolactin; se, selenium.

Setting	RCT Y/N	Intervention (duration)	Main Outcome parameters	Beneficial/ positive (endpoints)	Harmful	Reference
A						
Children after cardiopulmonary bypass surgery, range 2 days – 10.4 years (n=40)	Y	T3, 2µg/kg iv at day 1 after surgery and 1 µg/kg for 12 days	Cardiac function, ICU measures	Y	N	[77]
Premature newborns less than 37 GA (n=100)	N	LT4 (25 µg/day) plus T3 (5 µg/day) oral (once)	Mortality	Y	N	[78]
Premature newborns less than 32 weeks of GA (n=49)	Y	LT4, 10 (iv) or 20 µ/kg (through nasogastric tube) for 21 days	Chronic lung disease, death, CNS damage, sepsis	N	N	[79]
Children < 18 yrs with cessation of neurologic function during evaluation for organ recovery (n=171)	N	Weight based LT4 bolus followed by infusion	Vasopressor score	Y	N	[80]
B						
Protracted critical illness (n=14)	Y	TRH (1 µg/kg/h) iv plus GHRP-2 (1 µg/kg/h) iv for 5 days	GH and TSH secretion; biochemical anabolism/catabolism parameters	Y	N	[10]
Critical illness (n=76)	Y	GHRP-2, alone or in combination with TRH and GHRH (each peptide 1 µg/kg/h)	Synchrony among GH, TSH and PRL release	Y	N	[73]
Critical illness (n=40)	Y	Combinations of GHRH, GHRP-2 (both 1 µg/kg), TRH (200 µg) given as bolus, time interval 6h	Serum GH, TSH, T3 and T4 concentrations	Y	N	[74]
Protracted critical illness (n=20)	Y	Combinations of GHRH, GHRP-2, TRH start with bolus 1 µg/kg followed by 1 µg/kg/h (two consecutive nights)	Serum hormone concentrations	Y	N	[75]
Protracted critical illness (n=33)	Y	Combinations of GHRH, GHRP-2, TRH (each 1 µg/kg/h), GnRH (0,1µg/kg/90 min) for 5 days	Serum hormone and metabolic marker concentrations	Y	N	[76]

Elective coronary bypass surgery (n=80)	Y	T3 (125 µg/day) orally (7 days pre-op until discharge)	Hemodynamic data, morbidity and mortality	Y (hemodynamic parameters) N (morbidity, mortality)	N	63
Burn injury (n=36)	Y	T3 (200 µg/day orally or nasogastric tube in 4 divided doses until wounds were healed	Mortality, resting metabolic rate	N	N	62
Coronary bypass surgery (n=60)	Y	T3 (0,8µg/kg) iv for 6 h	Operative outcome, morbidity, mortality	N	N	64
Coronary bypass surgery (n=100)	Y	T3 (20 µg/12h) oral (48 h)	Serum T3, hemodynamic variables, morbidity	N	N	65
High risk valvular heart surgery (n=50)	Y	T3 (20 µg/12h) oral (24 h)	Vasopressor need	Y	N	66
Medical ICU patients with low T4 (n=23)	Y	1,5 µg/kg BW LT4 iv (2 weeks)	Mortality	N	N	67
Acute renal failure (n=59)	y	LT4 infusion, 150 µg/20 ml every 12h for 48h	% dialysis, % recovery, mortality	N	Y? (increased mortality)	61
Idiopathic dilated cardiomyopathie (n=20)	Y	100 µg LT4/day for 3 months	Cardiac performance	Y	N	71
Congestive heart failure (n=86)	Y	Thyroid hormone analogue DIPTA, 2/day, max dose 360 mg/day	Composite congestive heart failure endpoints	N	Y	72
NTIS after major trauma (n=31)	Y	Se (500 µg/day) with or without vitamin E and zinc supplement vs placebo (5 days)	Serum Se levels, T4 levels, duration of mechanical ventilation	Y (T4 and Se plasma levels) +/- (ventilation)	N	68
Septic ICU patients (n=40)	Y	High dose Se (158 µg/day, 3 days), followed by standard dose Se-selenite (31,6 µg/day)	Serum Se concentrations, oxidative damage parameters, need for renal replacement therapy	N	N	79

Legends

Figure 1: Schematic model of hypothalamic thyroid hormone signalling during inflammation. Inflammation activates the NfκB pathway in tanycytes, specialised cells lining the third ventricle (III). Tanycytes express D2, the main T3 producing enzyme in the brain, the promoter of which contains NfκB responsive elements. Binding of NfκB increases D2 expression and activity, and this stimulates the conversion of the prohormone T4 into T3. T3 will enter adjacent neurons and bind to neuronal TRs thereby regulating transcriptional activity of TRH.

Figure 2: Schematic model of cellular thyroid hormone metabolism. Cellular entry of TH is necessary for intracellular conversion and for exerting an effect via binding to the nuclear TR. Two categories of thyroid hormone transporters have been described, i.e., the organic anion transporters and the amino acid transporters. [1, 81-83] Once transported into the cell, thyroid hormones can be metabolized by outer or inner ring deiodination through the iodothyronine deiodinases. These enzymes belong to a selenocysteine containing enzyme family and comprise three types; type 1 (D1), 2 (D2) and type 3 (D3). [84] D1 is able to deiodinate the inner- and outer-ring of T4 as well as the outer ring of rT3. D1 is expressed in liver, kidney, thyroid and pituitary and localized in the plasma membrane.[85, 86] D2 is localized in the endoplasmic reticulum and deiodinates T4 into the biologically active T3. D2 is the main enzyme involved in the production of tissue T3 and therefore heavily involved in local thyroid hormone metabolism. [87, 88] D3 is localized in the plasma membrane and can be viewed as the major thyroid hormone inactivating enzyme, as it catalyses inner-ring deiodination of both T4 and T3, exclusively resulting in the production of biologically inactive rT3 and rT2. [21] The balance between D2 and D3 determines the availability of cellular T3 which enters the nucleus and binds to the nuclear receptor complex. Binding of T3 to the TR complex regulates transcriptional activity of T3-target genes.

Figure 3: Schematic representation of the effect of parental nutrition during NTIS. Critical illness-induced NTIS is characterized by low circulating T3 and elevation of rT3 levels. Low hypothalamic TRH mRNA expression, low circulating TSH and low T4 are also observed. When early full parenteral support is administered to resolve the caloric deficit, the peripheral changes in the thyroid axis partly normalize, but not its central suppression. [89]

Figure 4: Schematic and simplified overview of a variety of observed differential effects of NTIS on deiodinase activities within various tissues probably inducing inter-organ differences in T3 bioavailability in the presence of similarly decreased plasma T3.

Figure 5: Schematic representation of the variety of changes occurring during critical illness. Solid lines represent a causal relation, while a dashed line represents a probable effect. The scheme is based on both experimental and human studies. The net result of altered tissue TH metabolism may be beneficial or maladaptive, dependent on disease duration and severity.

References

1. Alkemade A, Friesema EC, Unmehopa UA, et al. Neuroanatomical pathways for thyroid hormone feedback in the human hypothalamus. *J Clin Endocrinol Metab* 2005; **90**(7): 4322-34.
2. Fekete C, Lechan RM. Negative feedback regulation of hypophysiotropic thyrotropin-releasing hormone (TRH) synthesizing neurons: role of neuronal afferents and type 2 deiodinase. *Front Neuroendocrinol* 2007; **28**(2-3): 97-114.
3. Boelen A, Kwakkel J, Fliers E. Beyond low plasma T3: local thyroid hormone metabolism during inflammation and infection. *Endocrine Rev* 2011; **32**(5): 670-93.
4. Wiersinga WM and van den Berghe G . Nonthyroidal illness syndrome. In: Braverman LE, Cooper D,S, ed. The Thyroid. 10 ed. Philadelphia: Lippincott Williams & Wilkins; 2013: 203-17.
5. Wartofsky L, Burman KD. Alterations in thyroid function in patients with systemic illness: the "euthyroid sick syndrome". *Endocrine Rev* 1982; **3**(2): 164-217.
6. Michalaki M, Vagenakis AG, Makri M, Kalfarentzos F, Kyriazopoulou V. Dissociation of the early decline in serum T(3) concentration and serum IL-6 rise and TNFalpha in nonthyroidal illness syndrome induced by abdominal surgery. *J Clin Endocrinol Metab* 2001; **86**(9): 4198-205.
7. Arem R TJ, Deppe SA. Comparison of thyroid hormone and cortisol measurements with APACHE II nad TISS scoring systems as predictors of mortality in the medical intensive care unit. *J Intensive Care Med* 1997; **12**(1): 12-7.
8. Gerdes AM, Iervasi G. Thyroid replacement therapy and heart failure. *Circulation* 2010; **122**(4): 385-93.
9. Van den Berghe G. Non-Thyroidal Illness in the ICU: A Syndrome with Different Faces. *Thyroid* 2014; **24**(10): 1456-65.
10. Van den Berghe G, Wouters P, Weekers F, et al. Reactivation of pituitary hormone release and metabolic improvement by infusion of growth hormone-releasing peptide and thyrotropin-releasing hormone in patients with protracted critical illness. *J Clin Endocrinol Metab* 1999; **84**(4): 1311-23.
11. Kaptein EM, Kaptein JS, Chang EI, Egodage PM, Nicoloff JT, Massry SG. Thyroxine transfer and distribution in critical nonthyroidal illnesses, chronic renal failure, and chronic ethanol abuse. *J Clin Endocrinol Metab* 1987; **65**(4): 606-16.
12. Boelen A, Wiersinga WM, Fliers E. Fasting-induced changes in the hypothalamus-pituitary-thyroid axis. *Thyroid* 2008; **18**(2): 123-9.
13. Arem R, Wiener GJ, Kaplan SG, Kim HS, Reichlin S, Kaplan MM. Reduced tissue thyroid hormone levels in fatal illness. *Metabolism* 1993; **42**(9): 1102-8.
14. Bello G, Pennisi MA, Montini L, et al. Nonthyroidal illness syndrome and prolonged mechanical ventilation in patients admitted to the ICU. *Chest* 2009; **135**(6): 1448-54.
15. Fliers E, Guldenaar SE, Wiersinga WM, Swaab DF. Decreased hypothalamic thyrotropin-releasing hormone gene expression in patients with nonthyroidal illness. *J Clin Endocrinol Metab* 1997; **82**(12): 4032-6.
16. Boelen A, Kwakkel J, Thijssen-Timmer DC, Alkemade A, Fliers E, Wiersinga WM. Simultaneous changes in central and peripheral components of the hypothalamus-pituitary-thyroid axis in lipopolysaccharide-induced acute illness in mice. *J Endocrinol* 2004; **182**(2): 315-23.
17. Fekete C, Gereben B, Doleschall M, et al. Lipopolysaccharide induces type 2 iodothyronine deiodinase in the mediobasal hypothalamus: implications for the nonthyroidal illness syndrome. *Endocrinology* 2004; **145**(4): 1649-55.
18. Lechan RM, Fekete C. Feedback regulation of thyrotropin-releasing hormone (TRH): mechanisms for the non-thyroidal illness syndrome. *J Endocrinol Invest* 2004; **27**(6 Suppl): 105-19.
19. Fliers E, Alkemade A, Wiersinga WM, Swaab DF. Hypothalamic thyroid hormone feedback in health and disease. *Prog Brain Res* 2006; **153**: 189-207.

20. Freitas BC, Gereben B, Castillo M, et al. Paracrine signaling by glial cell-derived triiodothyronine activates neuronal gene expression in the rodent brain and human cells. *J Clin Invest* 2010; **120**(6): 2206-17.
21. Gereben B, Zeold A, Dentice M, Salvatore D, Bianco AC. Activation and inactivation of thyroid hormone by deiodinases: local action with general consequences. *Cell Mol Life Sci* 2008; **65**(4): 570-90.
22. Peeters RP, Van der GS, Wouters PJ, et al. Tissue thyroid hormone levels in critical illness. *J Clin Endocrinol Metab* 2005; **90**(12): 6498-507.
23. Peeters RP, Wouters PJ, Kaptein E, Van Toor H, Visser TJ, G. VdB. Reduced activation and increased inactivation of thyroid hormone in tissues of critically ill patients. *J Clin Endocrinol Metab* 2003; **88**(7): 3202-11.
24. Olivares EL, Marassi MP, Fortunato RS, et al. Thyroid function disturbance and type 3 iodothyronine deiodinase induction after myocardial infarction in rats a time course study. *Endocrinology* 2007; **148**(10): 4786-92.
25. Huang SA, Bianco AC. Reawakened interest in type III iodothyronine deiodinase in critical illness and injury. *Nat Clin Pract Endocrinol Metab* 2008; **4**(3): 148-55.
26. Mooradian AD, Reed RL, Osterweil D, Schiffman R, Scuderi P. Decreased serum triiodothyronine is associated with increased concentrations of tumor necrosis factor. *J Clin Endocrinol Metab* 1990; **71**(5): 1239-42.
27. Chopra IJ, Sakane S, Teco GN. A study of the serum concentration of tumor necrosis factor-alpha in thyroidal and nonthyroidal illnesses. *J Clin Endocrinol Metab* 1991; **72**(5): 1113-6.
28. Pang XP, Hershman JM, Mirell CJ, Pekary AE. Impairment of hypothalamic-pituitary-thyroid function in rats treated with human recombinant tumor necrosis factor-alpha (cachectin). *Endocrinology* 1989; **125**(1): 76-84.
29. Palsson-McDermott EM, O'Neill LA. Signal transduction by the lipopolysaccharide receptor, Toll-like receptor-4. *Immunology* 2004; **113**(2): 153-62.
30. de Vries EM, Kwakkel J, Eggels L, et al. NFkappaB Signaling Is Essential for the Lipopolysaccharide-Induced Increase of Type 2 Deiodinase in Tanycytes. *Endocrinology* 2014; **155**(5): 2000-8.
31. Zeold A, Doleschall M, Haffner MC, et al. Characterization of the nuclear factor-kappa B responsiveness of the human dio2 gene. *Endocrinology* 2006; **147**(9): 4419-29.
32. Kwakkel J, Wiersinga WM, Boelen A. Differential involvement of nuclear factor-kappaB and activator protein-1 pathways in the interleukin-1beta-mediated decrease of deiodinase type 1 and thyroid hormone receptor beta1 mRNA. *J Endocrinol* 2006; **189**(1): 37-44.
33. Boelen A, Kwakkel J, Alkemade A, et al. Induction of type 3 deiodinase activity in inflammatory cells of mice with chronic local inflammation. *Endocrinology* 2005; **146**(12): 5128-34.
34. Kwakkel J, Surovtseva OV, de Vries EM, Stap J, Fliers E, Boelen A. A novel role for the thyroid hormone activating enzyme type 2 deiodinase in the inflammatory response of macrophages. *Endocrinology* 2014: en20132066.
35. Barca-Mayo O, Liao XH, DiCosmo C, et al. Role of type 2 deiodinase in response to acute lung injury (ALI) in mice. *Proc Natl Acad Sci U S* 2011; **108**(49): E1321-9.
36. Peeters RP, Wouters PJ, H. vT, Kaptein E, Visser TJ, G. VdB. Serum 3,3',5'-triiodothyronine (rT3) and 3,5,3'-triiodothyronine/rT3 are prognostic markers in critically ill patients and are associated with postmortem tissue deiodinase activities. *J Clin Endocrinol Metab* 2005; **90**(8): 4559-65.
37. Kwakkel J, van Beeren HC, Ackermans MT, et al. Skeletal muscle deiodinase type 2 regulation during illness in mice. *J Endocrinol* 2009; **203**(2): 263-70.
38. Rodriguez-Perez A, Palos-Paz F, Kaptein E, et al. Identification of molecular mechanisms related to nonthyroidal illness syndrome in skeletal muscle and adipose tissue from patients with septic shock. *Clin Endocrinol(Oxf)* 2008; **68**(5): 821-7.

39. Vanhorebeek I, De VR, Mesotten D, Wouters PJ, De Wolf-Peeters C, Van den BG. Protection of hepatocyte mitochondrial ultrastructure and function by strict blood glucose control with insulin in critically ill patients. *Lancet* 2005; **365**(9453): 53-9.
40. Weitzel JM, Iwen KA. Coordination of mitochondrial biogenesis by thyroid hormone. *Mol Cell Endocrinol* 2011; **342**(1-2): 1-7.
41. Harper ME, Seifert EL. Thyroid hormone effects on mitochondrial energetics. *Thyroid* 2008; **18**(2): 145-56.
42. Moreno M, de LP, Lombardi A, Silvestri E, Lanni A, Goglia F. Metabolic effects of thyroid hormone derivatives. *Thyroid* 2008; **18**(2): 239-53.
43. Boelen A, Boorsma J, Kwakkel J, et al. Type 3 deiodinase is highly expressed in infiltrating neutrophilic granulocytes in response to acute bacterial infection. *Thyroid* 2008; **18**(10): 1095-103.
44. Boelen A, Kwakkel J, Wieland CW, St Germain DL, Fliers E, Hernandez A. Impaired bacterial clearance in type 3 deiodinase-deficient mice infected with Streptococcus pneumoniae. *Endocrinology* 2009; **150**(4): 1984-90.
45. Klebanoff SJ. Iodination of bacteria: a bactericidal mechanism. *J Exp Med* 1967; **126**(6): 1063-78.
46. Schutz P, Bally M, Stanga Z, Keller U. Loss of appetite in acutely ill medical inpatients: physiological response or therapeutic target? *Swiss Med Weekly* 2014; **144**: w13957.
47 Fekete C, Lechan RM. Central regulation of hypothalamic-pituitary-thyroid axis under physiological and pathophysiological conditions. *Endocrine Rev* 2014; **35**(2): 159-94.
48. Galton VA, Hernandez A, St Germain DL. The 5-Deiodinases are Not Essential for the Fasting-induced Decrease in Circulating Thyroid Hormone Levels in Male Mice: Possible Roles for the Type 3 Deiodinase and Tissue Sequestration of Hormone. *Endocrinology* 2014: en20131884.
49. Richmand DA, Molitch ME, O'Donnell TF. Altered thyroid hormone levels in bacterial sepsis: the role of nutritional adequacy. *Metabolism* 1980; **29**(10): 936-42.
50. Chourdakis M, Kraus MM, Tzellos T, et al. Effect of early compared with delayed enteral nutrition on endocrine function in patients with traumatic brain injury: an open-labeled randomized trial. *J Parenter Enteral Nutr* 2012; **36**(1): 108-16.
51. Ouchi K, Matsubara S, Matsuno S. Effects of supplementary parenteral nutrition on thyroid hormone patterns in surgical patients with liver cirrhosis. *Nutrition* 1991; **7**(3): 189-92.
52. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. *N Eng J Med* 2011; **365**(6): 506-17.
53. Langouche L, Vander Perre S, Marques M, et al. Impact of early nutrient restriction during critical illness on the nonthyroidal illness syndrome and its relation with outcome: a randomized, controlled clinical study. *J Clin Endocrinol Metab* 2013; **98**(3): 1006-13.
54. Vlasselaers D, Milants I, Desmet L, et al. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. *Lancet* 2009; **373**(9663): 547-56.
55. Gielen M, Mesotten D, Wouters PJ, et al. Effect of tight glucose control with insulin on the thyroid axis of critically ill children and its relation with outcome. *J Clin Endocrinol Metab* 2012; **97**(10): 3569-76.
56. Barrett NA, Jones A, Whiteley C, Yassin S, McKenzie CA. Management of long-term hypothyroidism: a potential marker of quality of medicines reconciliation in the intensive care unit. *Int J Pharm Practice* 2012; **20**(5): 303-6.
57. Ringel MD. Management of hypothyroidism and hyperthyroidism in the intensive care unit. *Crit Care Clin* 2001; **17**(1): 59-74.
58. Fliers E, Wiersinga WM. Myxedema coma. *Rev Endocrin Metab Dis* 2003; **4**(2): 137-41.
59. Papi G, Corsello SM, Pontecorvi A. Clinical concepts on thyroid emergencies . *Front Endocrinol* 2014; **5** (102)
60. Angell TE, Lechner MG, Nguyen CT, Salvato VL, Nicoloff JT, LoPresti JS. Clinical Features and Hospital Outcomes in Thyroid Storm: A Retrospective Cohort Study. *J Clin Endocrinol Metab* 2014: jc20142850.

61. Acker CG, Singh AR, Flick RP, Bernardini J, Greenberg A, Johnson JP. A trial of thyroxine in acute renal failure. *Kidney Int* 2000; **57**(1): 293-8.
62. Becker RA, Vaughan GM, Ziegler MG, et al. Hypermetabolic low triiodothyronine syndrome of burn injury. *Crit Care Med* 1982; **10**(12): 870-5.
63. Sirlak M, Yazicioglu L, Inan MB, et al. Oral thyroid hormone pretreatment in left ventricular dysfunction. *Eur J Cardiothorac Surg* 2004; **26**(4): 720-5.
64. Guden M, Akpinar B, Saggbas E, Sanisoglu I, Cakali E, Bayindir O. Effects of intravenous triiodothyronine during coronary artery bypass surgery. *Asian Cardiovasc Thorac Ann* 2002; **10**(3): 219-22.
65. Choi YS, Shim JK, Song JW, Song Y, Yang SY, Kwak YL. Efficacy of perioperative oral triiodothyronine replacement therapy in patients undergoing off-pump coronary artery bypass grafting. *J Cardiothorac Vasc Anesth* 2013; **27**(6): 1218-23.
66. Choi YS, Kwak YL, Kim JC, Chun DH, Hong SW, Shim JK. Peri-operative oral triiodothyronine replacement therapy to prevent postoperative low triiodothyronine state following valvular heart surgery. *Anaesthesia* 2009; **64**(8): 871-7.
67. Brent GA, Hershman JM. Thyroxine therapy in patients with severe nonthyroidal illnesses and low serum thyroxine concentration. *J Clin Endocrinol Metab* 1986; **63**(1): 1-8.
68. Berger MM, Reymond MJ, Shenkin A, et al. Effect of selenium supplements on the low T3 syndrome after trauma: A randomized trial. *Intensive Care Medicine*, 1996; **22**(6): 575-81.
69. Mishra V, Baines M, Perry SE, et al. Effect of selenium supplementation on biochemical markers and outcome in critically ill patients. *Clin Nutr* 2007; **26**(1): 41-50.
70. Vidart J, Wajner SM, Leite RS, et al. N-acetylcysteine administration prevents nonthyroidal illness syndrome in patients with acute myocardial infarction: a randomized clinical trial. *J Clin Endocrinol Metab* 2014; **99**(12): 4537-45.
71. Moruzzi P, Doria E, Agostoni PG. Medium-term effectiveness of L-thyroxine treatment in idiopathic dilated cardiomyopathy. *Am J Med* 1996; **101**(5): 461-7.
72. Goldman S, McCarren M, Morkin E, et al. DITPA (3,5-Diiodothyropropionic Acid), a thyroid hormone analog to treat heart failure: phase II trial veterans affairs cooperative study. *Circulation* 2009; **119**(24): 3093-100.
73. Van den Berghe G, Wouters P, Bowers CY, de Zegher F, Bouillon R, Veldhuis JD. Growth hormone-releasing peptide-2 infusion synchronizes growth hormone, thyrotrophin and prolactin release in prolonged critical illness. *Eur J Endocrinol* 1999; **140**(1): 17-22.
74. Van den Berghe G, de Zegher F, Bowers CY, et al. Pituitary responsiveness to GH-releasing hormone, GH-releasing peptide-2 and thyrotrophin-releasing hormone in critical illness. *Clin Endocrinol (Oxf)* 1996; **45**(3): 341-51.
75. Van den Berghe G, de Zegher F, Baxter RC, et al. Neuroendocrinology of prolonged critical illness: effects of exogenous thyrotropin-releasing hormone and its combination with growth hormone secretagogues. *J Clin Endocrinol Metab* 1998; **83**(2): 309-19.
76. Van den Berghe G, Baxter RC, Weekers F, et al. The combined administration of GH-releasing peptide-2 (GHRP-2), TRH and GnRH to men with prolonged critical illness evokes superior endocrine and metabolic effects compared to treatment with GHRP-2 alone. *Clin Endocrinol (Oxf)* 2002; **56**(5): 655-69.
77. Bettendorf M, Schmidt KG, Grulich-Henn J, Ulmer HE, Heinrich UE. Tri-iodothyronine treatment in children after cardiac surgery: a double-blind, randomised, placebo-controlled study. *Lancet* 2000; **356**(9229): 529-34.
78. Schonberger W, Grimm W, Emmrich P, Gempp W. Reduction of mortality rate in premature infants by substitution of thyroid hormones. *Eur J Pediatr* 1981; **135**(3): 245-53.
79. Smith LM, Leake RD, Berman N, Villanueva S, Brasel JA. Postnatal thyroxine supplementation in infants less than 32 weeks' gestation: effects on pulmonary morbidity. *J Perinatol* 2000; **20**(7): 427-31.

80. Zuppa AF, Nadkarni V, Davis L, et al. The effect of a thyroid hormone infusion on vasopressor support in critically ill children with cessation of neurologic function. *Crit Care Med* 2004; **32**(11): 2318-22.
81. Sugiyama D, Kusuhara H, Taniguchi H, et al. Functional characterization of rat brain-specific organic anion transporter (Oatp14) at the blood-brain barrier: high affinity transporter for thyroxine. *J Biol Chem* 2003; **278**(44): 43489-95.
82. Heuer H, Maier MK, Iden S, et al. The monocarboxylate transporter 8 linked to human psychomotor retardation is highly expressed in thyroid hormone-sensitive neuron populations. *Endocrinology* 2005; **146**(4): 1701-6.
83. Visser WE, Friesema EC, Visser TJ. Minireview: thyroid hormone transporters: the knowns and the unknowns. *Mol Endocrinol* 2011; **25**(1): 1-14.
84. Kohrle J. The deiodinase family: selenoenzymes regulating thyroid hormone availability and action. *Cell Mol Life Sci* 2000; **57**(13-14): 1853-63.
85. Jakobs TC, Schmutzler C, Meissner J, Kohrle J. The promoter of the human type I 5'-deiodinase gene--mapping of the transcription start site and identification of a DR+4 thyroid-hormone-responsive element. *Eur J Biochem* 1997; **247**(1): 288-97.
86. Toyoda N, Zavacki AM, Maia AL, Harney JW, Larsen PR. A novel retinoid X receptor-independent thyroid hormone response element is present in the human type 1 deiodinase gene. *Mol Cell Biol* 1995; **15**(9): 5100-12.
87. Burmeister LA, Pachucki J, St Germain DL. Thyroid hormones inhibit type 2 iodothyronine deiodinase in the rat cerebral cortex by both pre- and posttranslational mechanisms. *Endocrinology* 1997; **138**(12): 5231-7.
88. Sagar GD, Gereben B, Callebaut I, et al. Ubiquitination-induced conformational change within the deiodinase dimer is a switch regulating enzyme activity. *Mol Cell Biol* 2007; **27**(13): 4774-83.
89. Casaer MP, Van den Berghe G. Nutrition in the acute phase of critical illness. *N Engl J Med* 2014; **370**(25): 2450-1.

Figure

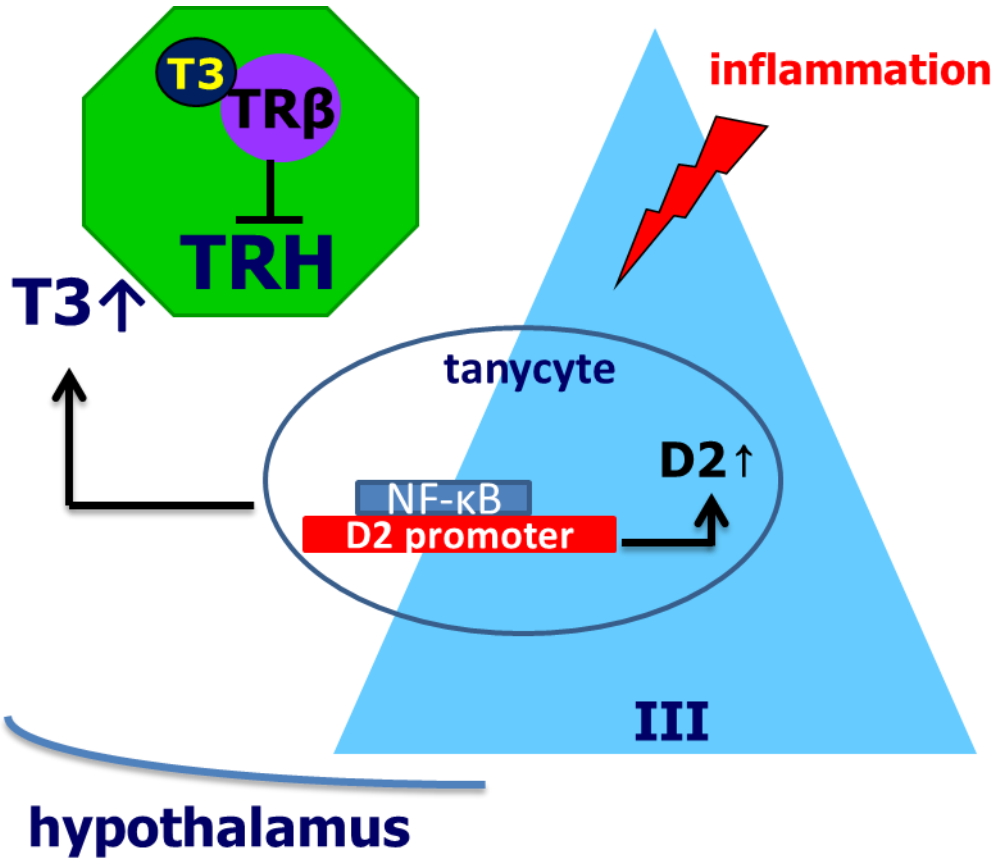

Figure 1

figure

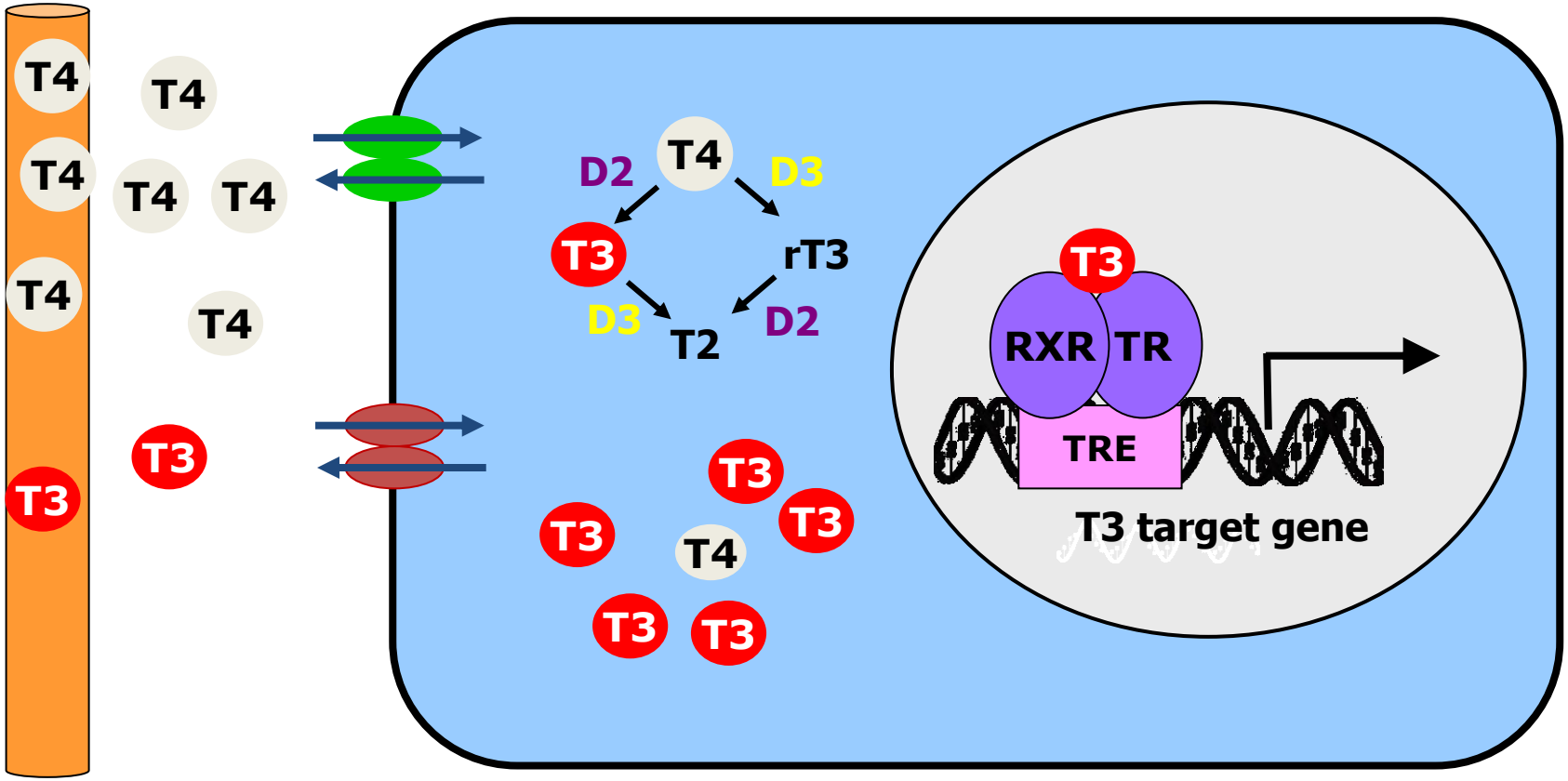

Figure 2

Figure

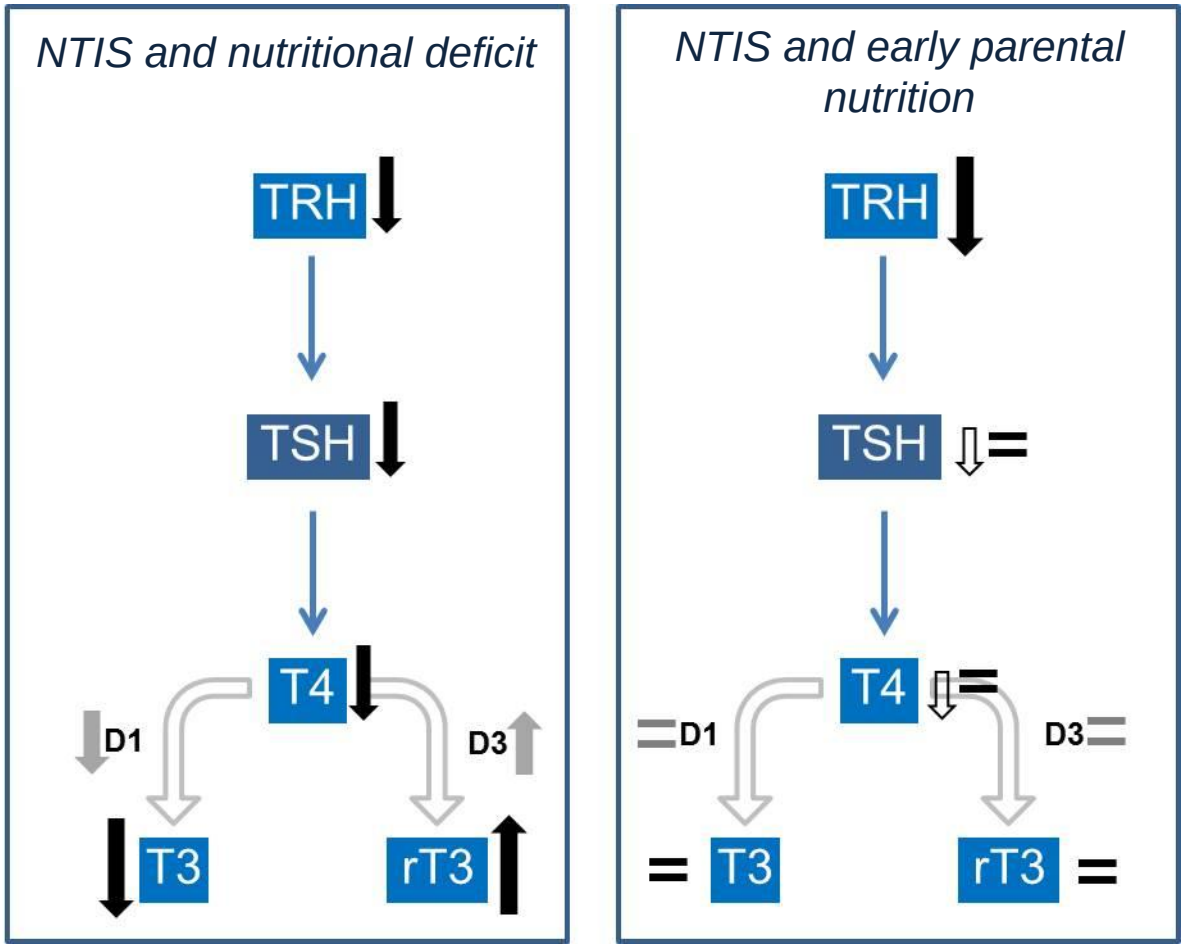

Figure 3

Figure

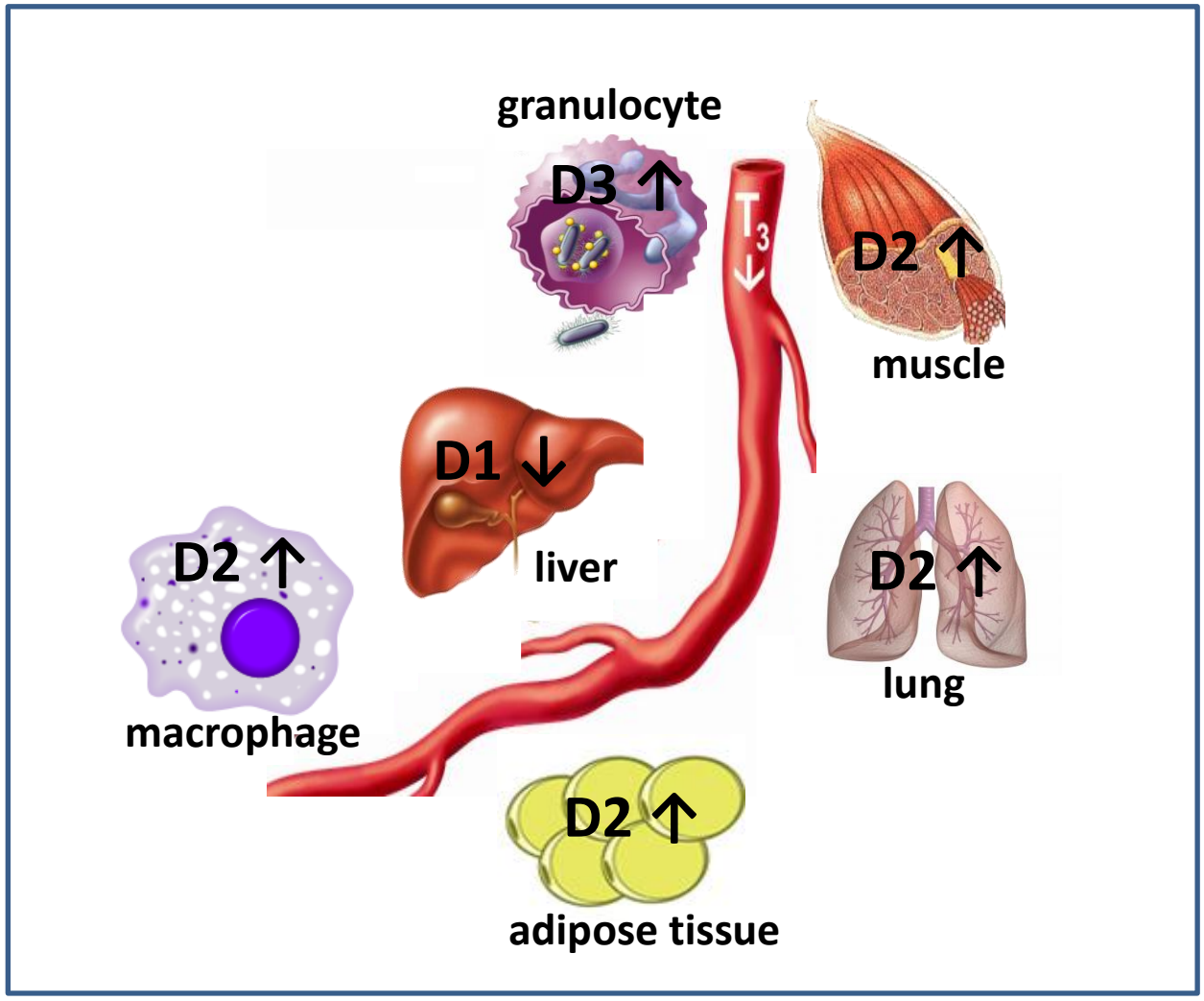

Figure 4

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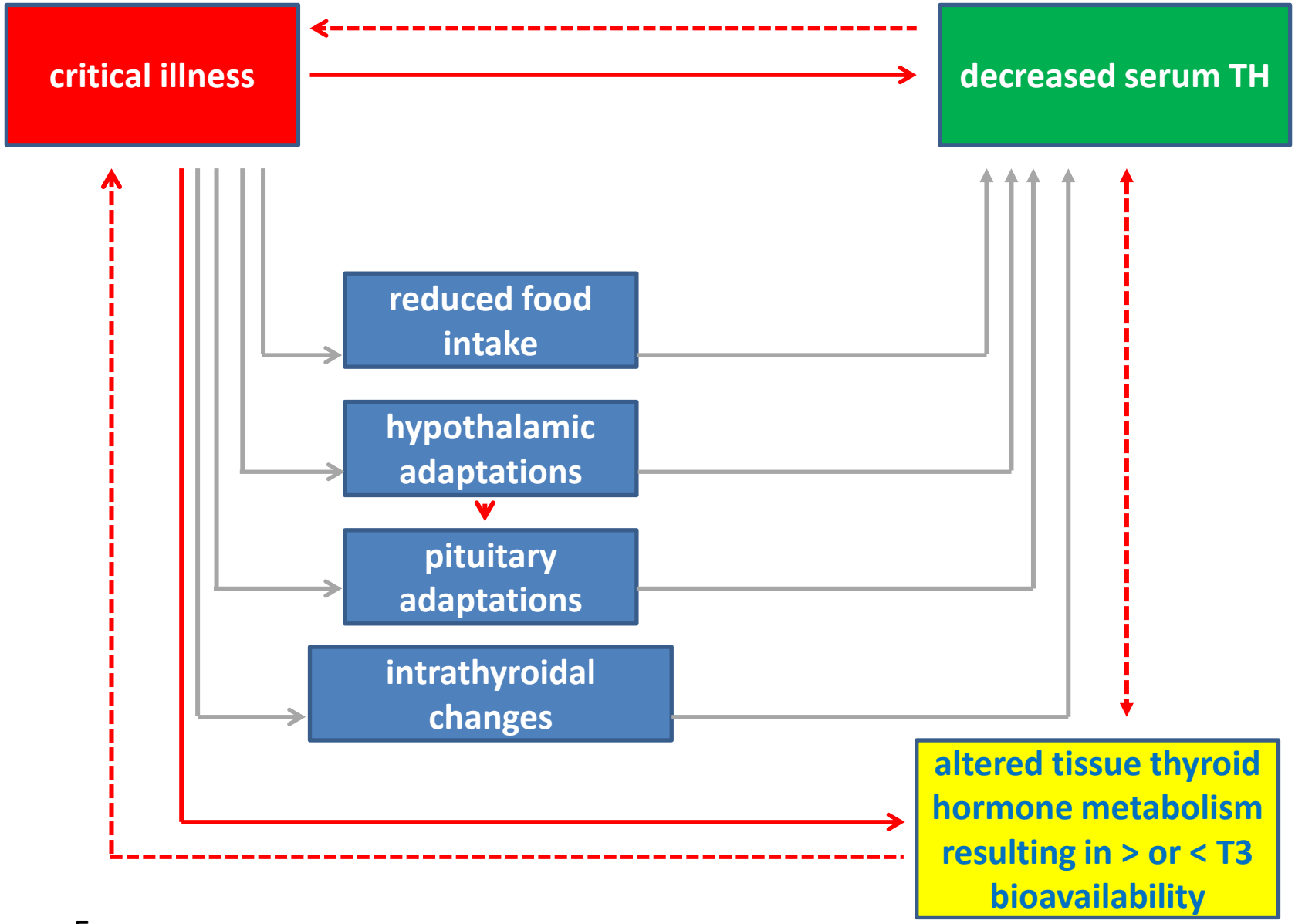

Figure 5